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Lanthanide Complexes | *Very Important Paper* |

VIP Definition of the Labile Capping Bond Effect in Lanthanide Complexes

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Abstract: Two macrocyclic ligands containing a cyclen unit, a methyl group, a picolinate arm, and two acetate pendant arms attached to two nitrogen atoms of the macrocycle either in *trans* (1,7-H_3Medo2ampa = 2,2′-(7-((6-carboxypyridin-2-yl)methyl)-10-methyl-1,4,7,10-tetraazacyclododecane-1,4-diyl)diacetic acid) or in *cis* (1,4-H_3Medo2ampa) positions are reported. These ligands provide eight-coordination to the Ln^{3+} ions, leaving a coordination position available for a water molecule that occupies a capping position in the twisted square antiprismatic polyhedron (1,4-H_3Medo2ampa) or one of the positions of the square antiprism (1,7-H_3Medo2ampa). The charge neutral [Gd(1,7-Medo2ampa)] complex presents an unprecedentedly low water-exchange rate ($k_{ex}^{298} = 8.8 \times 10^3\ s^{-1}$), whereas water exchange in [Gd(1,4-Medo2ampa)] is three orders of magnitude faster ($k_{ex}^{298} = 6.6 \times 10^6\ s^{-1}$). These results showcase the labile capping bond phenomenon: A ligand occupying a capping position is hindered by the environment and thus is intrinsically labile.

Introduction

Exchange reactions involving water molecules in the first and second solvation shells of metal complexes are of fundamental importance to understand the reactivity of metal ions in both chemical and biological systems.[1] The replacement of a coordinated water molecule by an entering ligand represents a key step in the formation of metal complexes in aqueous solutions[2] and in many redox processes.[3] The mean residence times of coordinated water molecules in aquated complexes spread over 20 orders of magnitude from approximately 300 years for $[Ir(H_2O)_6]^{3+}$ to only approximately 200 ps for the extremely labile $[Eu(H_2O)_7]^{2+}$ (at 25 °C).[4,5]

The water-exchange reactions in aquated lanthanide ions $[Ln(H_2O)_q]^{3+}$ ($q = 8$ or 9) were investigated by Merbach and coworkers using ^{17}O NMR techniques.[6] Among the different Ln^{3+} ions, Gd^{3+} complexes have attracted particular attention during the last 20 years owing to their increasing use as contrast agents (CAs) in clinical and pre-clinical magnetic resonance imaging (MRI) procedures.[7] CAs are paramagnetic compounds, often small Gd^{3+} chelates, that accelerate the relaxation rates of water molecules in the surrounding tissues.[8] Water-exchange dynamics play a key role in determining the effectiveness of Gd^{3+} CAs, as exchange of the bound water molecule(s) should be sufficiently fast to attain optimal relaxivities.[9] However, extremely slow water-exchange rates in Ln^{3+} complexes have been exploited to design CAs based on the chemical exchange saturation transfer (CEST) approach, which represent attractive alternatives to the classical Gd^{3+}-based agents.[10] CEST agents based on Ln^{3+} ions typically contain a pool of exchangeable protons in intermediate-to-slow condition with the bulk water ($k_{ex} \leq \Delta\omega$, where $\Delta\omega$ is the frequency difference). Application of a presaturation pulse at the frequency of the exchangeable protons (i.e., a coordinated water molecule) induces the transfer of some saturated spins into the water pool, thereby attenuating the signal of bulk water.[11]

The residence time of a water molecule in the inner coordination sphere of Gd^{3+} complexes (τ_m^{298}) expands over a range of approximately four orders of magnitude from the longest determined for dota-tetraamide (dota = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) derivatives ($\tau_m^{298} = 8$–20 μs)[12] to the shortest measured for the aqua ion[13] and

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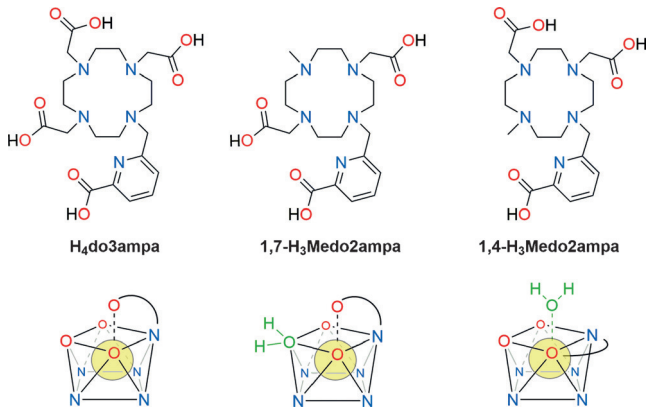
a Gd^{3+} complex with an octadentate ligand containing phosphonate groups ($\tau_m^{298} \approx 1.3–1.4$ ns).[14] In the case of Eu^{3+}-based CEST agents, appropriate ligand modifications make it possible to attain residence times as long as 150–700 μs.[15,16]

Among the different factors that were identified to accelerate the water exchange of the coordinated water molecule in Gd^{3+} (or Eu^{3+}) complexes are 1) increasing the negative charge of the complex,[17] and 2) increasing the steric compression around the water coordination site.[18] Both effects facilitate the departure of the coordinated water molecule in a dissociative process, which is the most common mechanism responsible for the water-exchange reaction in nine-coordinate Gd^{3+} complexes.[1] On the contrary, the inclusion of hydrophobic units around the water binding site minimizes hydrogen-bonding between the coordinated water and the second coordination sphere, which results in slower water-exchange rates.[16,19] The wider and more extensive number of studies focused on monoaqua nine-coordinated complexes. Many of these are derivatives of dota in which the water molecule occupies the apical position, capping the upper square face of the antiprism. A common and effective strategy for improving the effectiveness of a Gd^{3+}-chelate as MRI probe is to increase the hydration state from one ($q=1$) to two ($q=2$). In dota-like derivatives, this implies the presence of one water molecule in the axial position and of a second water molecule in an equatorial position, orthogonal to the first. A relevant yet still unanswered question concerning the water-exchange dynamics of these systems arises: Do the two water molecules show similar rates of exchange or do they behave independently?

Thus, we sought to design a pair of ligands for Ln^{3+} complexation having an identical number and type of donor atoms and providing complexes containing a coordinated water molecule either occupying a position in the coordination polyhedron or a capping position. This was accomplished by using as a starting point the H_4do3ampa ligand (H_4do3ampa = 2,2′,2″-(10-((6-carboxypyridin-2-yl)methyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid, Scheme 1),[20] which was shown to form nine-coordinate complexes in solution in which the oxygen atom of the picolinate group occupies the capping position in a capped square antiprismatic (SAP) coordination polyhedron. We hypothesized that removing one of the carboxylate groups in *trans* position to the picolinate arm to afford 1,7-H_3Medo2ampa should result in the coordination of a water molecule in one of the square faces of the coordination polyhedron, with the capping position occupied by the oxygen atom of the picolinate group. In contrast, removal of a carboxylate group in *cis* position with respect to the pyridyl unit should allow picolinate to lean on the methyl group, permitting a water molecule to occupy a capping position. Thus, we report the synthesis of the 1,7-H_3Medo2ampa and 1,4-H_3Medo2ampa ligands, and demonstrate the labile capping bond effect with a detailed analysis of the water-exchange rates in the corresponding Gd^{3+} complexes. The discovery of this effect provides new strategies to modulate ligand-exchange rates in Ln^{3+} complexes, with great potential impact in the coordination chemistry of the 4f elements.

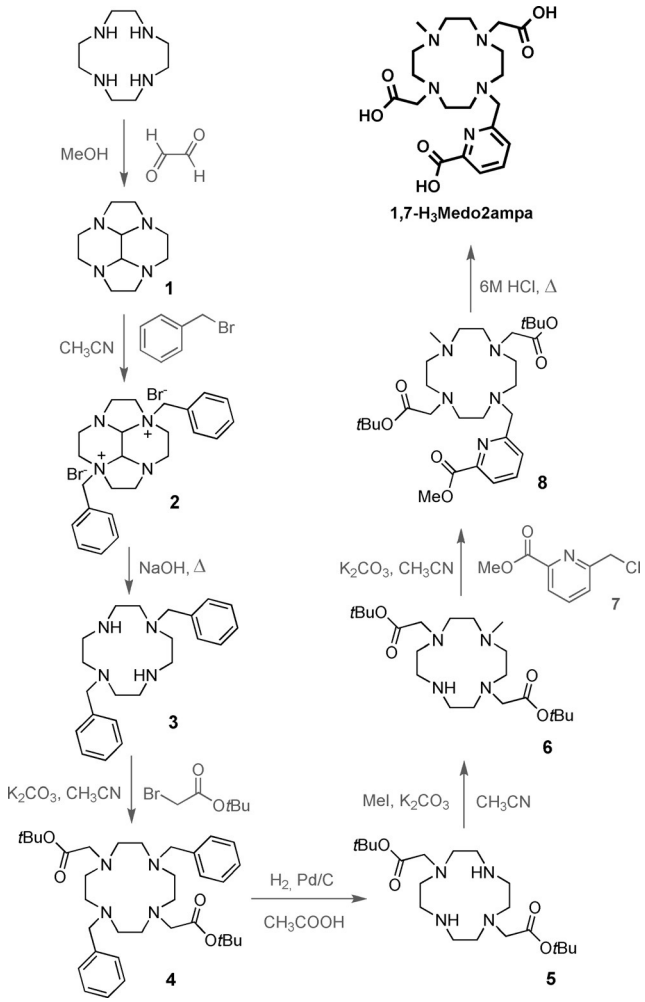


Scheme 1. Ligands discussed in the present work and their expected coordination mode after complexation with Gd^{3+}.

Results and Discussion

Synthesis of the ligands and metal complexes

The synthetic protocol used for the preparation of 1,7-H_3Medo2ampa is shown in Scheme 2. Cyclen glyoxal (**1**) was obtained following the literature procedure by direct conden-



Scheme 2. Synthesis of 1,7-H_3Medo2ampa.

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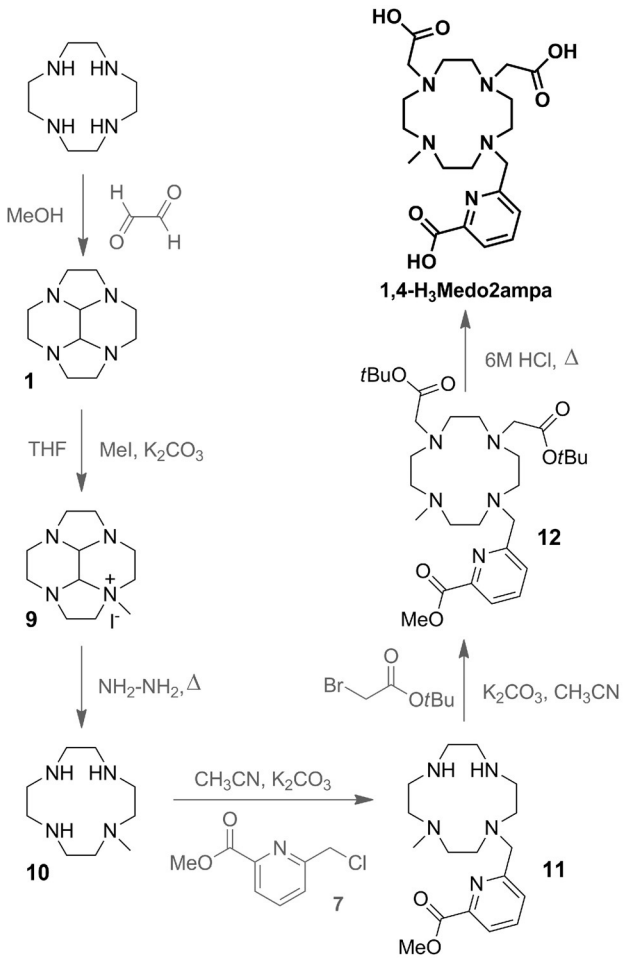
sation of glyoxal with cyclen.[21] The subsequent *trans*-alkylation of **1** with benzyl bromide afforded compound **2**,[22] which was deprotected under basic conditions to furnish compound **3** with an overall yield of 93% over the three steps. Reaction of **3** with *tert*-butyl bromoacetate in acetonitrile in the presence of K_2CO_3 afforded compound **4** in satisfactory yield (72%). The benzyl groups of **4** were removed by Pd-catalyzed hydrogenolysis to yield compound **5** quantitatively. Monoalkylation of **5** with MeI to afford the key intermediate **6** was then achieved with 92% yield. Careful selection of the reaction conditions was critical for the preparation of this compound in high yield. In particular, yields increased significantly if the reaction was performed at low temperature (0 °C), the concentration of precursor **5** in the reaction medium was not too high (< 0.02 M), and MeI was added slowly to the solution of **5**. Alkylation of **6** with the 6-chloromethyl derivative **7**[23] followed by deprotection of the methyl and *tert*-butyl ester groups provided the 1,7-H_3Medo2ampa ligand, which was isolated as the hydrochloride salt with an overall yield of 50% as calculated from cyclen (eight steps). The hydrochloride salt was then converted to the trifluoroacetate salt by treating the former with trifluoroacetic acid.

Reaction of 1,7-H_3Medo2ampa with lanthanide triflates in the presence of an excess of triethylamine resulted in the formation of the charge-neutral complexes of formula [Ln(1,7-Medo2ampa)(H_2O)] (Ln = La, Eu, Gd, Tb, Yb, or Lu), which were isolated in 85–90% yield. The high-resolution mass spectra (HR-MS, ESI^+) show peaks resulting from the [Ln(1,7-HMedo2ampa)]$^+$ entities, thereby confirming the formation of the complexes (Figures S17–S22, Supporting Information).

The synthesis of 1,4-H_3Medo2ampa (Scheme 3) started with the conversion of **1** into the methylated derivative **9** by reaction with MeI (97%)[22] followed by deprotection with hydrazine hydrate (87%). Subsequently, compound **10** was alkylated with compound **7**, affording the *cis* derivative **11**, which was used without further purification in the next step. Previous studies showed that the regioselective *cis* alkylation of cyclen depended both on the steric hindrance of electrophiles and the solvent system.[24] The regioselective alkylation of **10** was achieved in acetonitrile at 0 °C. Finally, reaction of **11** with *tert*-butyl bromoacetate in acetonitrile in the presence of K_2CO_3 followed by deprotection of the methyl and *tert*-butyl ester groups with 6 M HCl provided the 1,4-H_3Medo2ampa ligand in its hydrochloride salt form. The overall yield over the six steps required to prepare the ligand starting from cyclen was 31%. The [Ln(1,7-Medo2ampa)] complexes were prepared in aqueous solution by mixing equimolar amounts of the ligand and lanthanide chlorides or triflates, followed by adjustment of the pH value to 7.0. The HR-MS spectra (ESI^+) confirm the formation of the complexes.



Scheme 3. Synthesis of 1,4-H_3Medo2ampa.

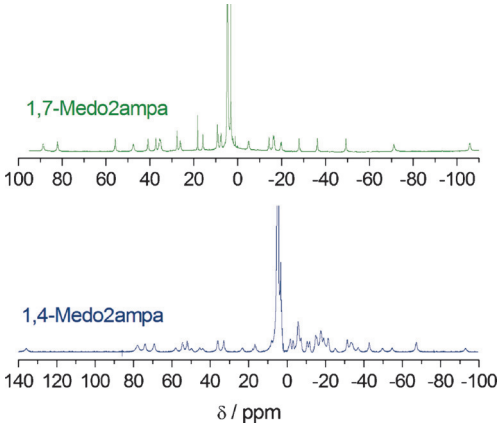


Figure 1. ^{1}H NMR spectra (300 MHz, D_2O, pH 7.0) of the Yb^{3+} complexes of 1,7-Medo2ampa^{3-} and 1,4-Medo2ampa^{3-}.

Structural analysis

The ^{1}H NMR spectrum of the paramagnetic [Yb(1,7-Medo2ampa)] complex (Figure 1) shows 25 of the 26 paramagnetically shifted signals expected for a single species with C_1 symmetry in solution. The most shifted axial protons of the cyclen ring are observed at 88.9, 82.3, 56.0, and 47.7 ppm. These values are very similar to those observed previously for the [Yb(do3ampa)]$^-$ complex (99.7, 78.8, 61.5, and 57.0 ppm).[20] The latter compound was demonstrated to adopt an SAP structure in solution by analysis of the Yb^{3+}-induced ^{1}H NMR shifts. Thus, we conclude that the [Yb(1,7-Medo2ampa)] complex adopts a SAP structure in solution as well, which is confirmed

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by the relative energies of the two isomers obtained using DFT calculations (Supporting Information).

The ^{1}H NMR spectrum of the [Yb(1,4-Medo2ampa)] complex (Figure 1) reveals the presence of two complex species in solution, which provide two sets of signals with different intensities. The most shifted axial proton of the minor species (ca. 30%) is observed at 135.8 ppm, which is characteristic of a SAP coordination around the metal ions.[25] Thus, the speciation of [Yb(1,4-Medo2ampa)] in solution is dominated by the twisted-square antiprismatic (TSAP) isomer (ca. 70%).

The number of water molecules coordinated to the Ln^{3+} ion (q) was assessed by measuring the lifetimes of the $Eu^{3+}(^5D_0)$ and $Tb^{3+}(^5D_4)$ excited states in solutions of the complexes in H_2O and D_2O (Table 1).[26] The absorption spectra of the complexes recorded in H_2O solution show an absorption band with a maximum at 274 nm typical of the picolinate chromophore (Supporting Information).[20] The emission spectra recorded under excitation through the ligand bands (10^{-5} M, pH 7.0) show the $^5D_0 \rightarrow {}^7F_J$ ($J=0$–4) and $^5D_4 \rightarrow {}^7F_J$ ($J=3$–6) transitions characteristic of Eu^{3+} and Tb^{3+}, respectively (see the Supporting Information).

Table 1. Luminescence lifetimes τ [ms] and hydration numbers q of the Eu^{3+} and Tb^{3+} complexes of 1,7-Medo2ampa and 1,4-Medo2ampa.

	Ln^{3+}	$\tau(H_2O)$ [ms]	$\tau(D_2O)$ [ms]	Δk_{obs}[a]	q[b]
1,7-Medo2ampa	Eu^{3+}	0.569(3)	1.69(1)	1.17	1.1
	Tb^{3+}	1.793(5)	3.09(3)	0.23	0.9
1,4-Medo2ampa	Eu^{3+}	0.584(2)	1.327(4)	0.96	0.9
	Tb^{3+}	2.39(1)	2.76(1)	0.06	0.0

[a] $\Delta k_{obs} = k_{obs}(H_2O) - k_{obs}(D_2O)$; $k_{obs} = 1/\tau_{obs}$; [b] $q(Eu) = 1.2(\Delta k_{obs} - 0.25)$; $q(Tb) = 5.0(\Delta k_{obs} - 0.06)$.

The emission lifetimes of the $Eu^{3+}(^5D_0)$ and $Tb^{3+}(^5D_4)$ excited states of the complexes with 1,7-Medo2ampa^{3-} provide hydration numbers of $q=1.1$ and 0.9 according to the equation of Beeby.[27] These results indicate that the Ln^{3+} complexes of 1,7-do2ampa^{3-} contain a water molecule in the inner-coordination sphere. This shows that the complexes are nine-coordinated in aqueous solution owing to the octadentate binding of the ligand and the presence of a coordinated water molecule. Application of the same methodology to the complexes with 1,4-do2ampa^{3-} provides a hydration number of 0.9 for Eu^{3+} and a hydration number of 0.0 for Tb^{3+}. These results suggest a rather abrupt change of the hydration number at the center of the lanthanide series.

To gain more insight into the structure of the complexes in aqueous solution, we performed DFT calculations at the TPSSh/LCRECP/6-31G(d) level.[28–30] We have shown previously that a cluster/continuum approach including explicitly two second-sphere water molecules provides a satisfactory description of the Gd–O_{water} distances and accurate ^{17}O hyperfine coupling constants.[31] The minimum energy conformation calculated for the SAP isomer of the [Gd(1,7-Medo2ampa)(H_2O)]·2H_2O system (Figure 2) indicates octadentate binding of the ligand to the Gd^{3+} ion. The basal plane of the antiprism is described by the four nitrogen atoms of the cyclen unit, whereas the upper plane is defined by the nitrogen atom of the pyridyl unit, two oxygen atoms of the acetate pendant arms, and a coordinated water molecule. The oxygen atom of the picolinate group occupies the capping position. The mean twist angle of the upper and lower square faces amounts to 36.7°.

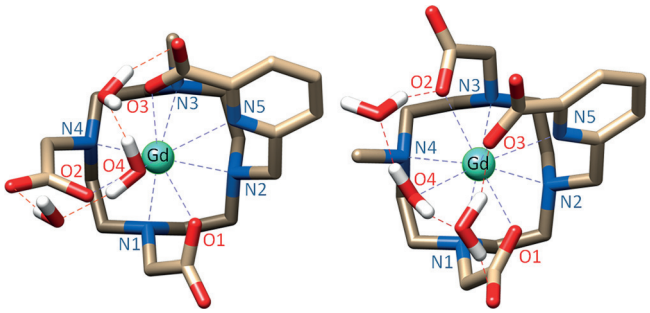

Figure 2. Structures of the [Gd(1,4-Medo2ampa)(H_2O)]·2H_2O (left) and [Gd(1,7-Medo2ampa)(H_2O)]·2H_2O (right) complexes optimized in aqueous solution at the TPSSh/LCRECP/6-31G(d) level.

Because the [Yb(1,4-Medo2ampa)] complex exists in solution as a mixture of SAP and TSAP isomers we initially performed calculations on the [Gd(1,4-Medo2ampa)(H_2O)] system. These calculations provided the SAP and TSAP isomers as minimum-energy conformations and predicted a rather small Gibbs energy difference between them, favoring the TSAP form by only approximately 2 kcal mol^{-1}. This energy reduces to 1.6 kcal mol^{-1} for the Eu^{3+} complex. Thus, it is likely that both the SAP and TSAP isomers are present in solution in the case of the Gd^{3+} complex. The broad signals observed in the ^{1}H NMR spectrum of the Eu^{3+} complex are in line with this hypothesis. Most likely the SAP isomer contains a water molecule coordinated to the Ln^{3+} ion, whereas the sterically more crowded TSAP isomer does not contain a coordinated water molecule. The latter species is largely dominating in the case of the Tb^{3+} complex, thus resulting in a q value of 0.0 (Table 1).

The optimized structure of the SAP isomer of the [Gd(1,4-Medo2ampa)(H_2O)]·2H_2O complex reveals octadentate binding of the ligand, with the coordinated water molecule occupying the capping position above the mean plane delineated by the four donor atoms of the pendant arms. The calculated Gd–O_{water} distance (2.549 Å) is considerably longer than that calculated for [Gd(1,7-Medo2ampa)(H_2O)]·2H_2O (2.476 Å). These data reflect a weaker binding of the water molecule if it occupies a capping position in the coordination polyhedron. The calculated electron densities at the bond critical points (ρ_{BCP}) of the Gd–O_{water} bonds (0.041 and 0.034 a.u. for the complexes with 1,7-Medo2ampa^{3-} and 1,4-Medo2ampa^{3-}, respectively) confirm that the coordinated water molecule is more tightly bound to the metal ion in the [Gd(1,7-Medo2ampa)(H_2O)] complex.[32]

Water-exchange rates of the coordinated water molecules

The water-exchange rates of the coordinated water molecules in the Gd^{3+} complexes were assessed by means of ^{17}O NMR

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transverse relaxation rates and chemical shifts and ^{1}H relaxivity measurements. A combined analysis of the ^{1}H relaxivity and ^{17}O NMR data is required for an accurate estimation of the water-exchange rates.[33]

The relaxivities (r_{1p}) of an aqueous solution of the complexes were first assessed at 20 MHz and 25 °C (Figure 3). The relaxivity of [Gd(1,7-Medo2ampa)] measured in the pH range 5.1–7.2 (1.94 mM^{-1}s^{-1}) is very low compared to the relaxivities of Gd^{3+}

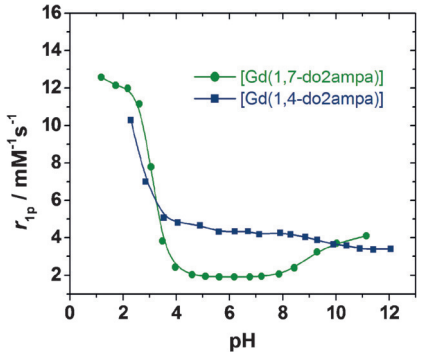

Figure 3. Plot of the ^{1}H relaxivities (20 MHz, 25 °C) of [Gd(1,7-Medo2ampa)] and [Gd(1,4-Medo2ampa)] as a function of pH value.

complexes containing one inner-sphere water molecule such as $[Gd(dota)]^-$. Below pH 5.1, r_{1p} increases owing to the dissociation of the complex, with a relaxivity observed at pH < 2 that is very similar to that of $[Gd(H_2O)]^{3+}$.[13] Increasing the pH value above 7.2 results in a noticeable increase of r_{1p}, which reaches a value of 4.1 mM^{-1}s^{-1} at pH 11.1. This pH dependence of r_{1p} is characteristic of systems with very slow water-exchange rates around neutral pH value, so that the observed relaxivity is the result of the outer-sphere mechanism. Increasing the pH value favors an acceleration of the water exchange by OH^- catalysis of prototropic exchange.[12,34] The relaxivity of [Gd(1,4-Medo2ampa)] at pH 7.0 (20 MHz and 25 °C) is 4.2 mM^{-1}s^{-1}, and therefore considerably higher than that of the *trans* derivative. Again relaxivity increases below pH ≈ 4 owing to complex dissociation. Above pH 8 the relaxivity decreases slightly, likely resulting from the formation of hydroxo complexes.[35]

Additional insight into the exchange dynamics of the coordinated water molecules in these Gd^{3+} complexes was obtained by measuring the temperature dependence of r_{1p} (20 MHz, Figure 4). The relaxivity of [Gd(1,4-Medo2ampa)] decreases with increasing temperature, a behavior typical of small chelates in which fast rotation of the complex in solution limits proton relaxivity. Conversely, the temperature dependence of r_{1p} measured for [Gd(1,7-Medo2ampa)] at 20 MHz presents two distinct regions. From 5 to 30 °C the relaxivity is determined by the outer-sphere contribution, which increases as the temperature is reduced, whereas in the temperature range of 40–80 °C r_{1p} remains almost constant. This can be explained by an increasing contribution of the inner-sphere mechanism arising from a reduced τ_m (acceleration of the water-exchange rate), which is compensated by a decrease of the outer-sphere contribution and a faster rotation of the complex in solution at high temperatures.

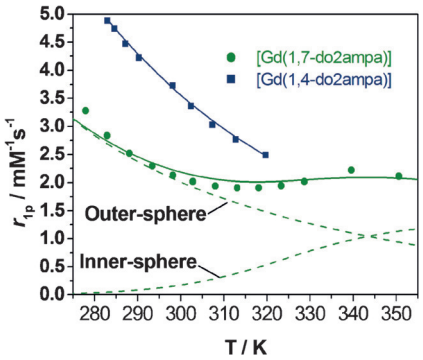

Figure 4. Plot of the ^{1}H relaxivities (20 MHz, pH 7) of [Gd(1,7-Medo2ampa)] and [Gd(1,4-Medo2ampa)] as a function of temperature. The solid lines represent the fits of the data as described in the text. The dotted lines represent the inner- and outer-sphere contributions calculated for [Gd(1,7-Medo2ampa)].

The ^{1}H nuclear magnetic relaxation dispersion (NMRD) profiles were recorded with aqueous solutions of the complexes in the proton Larmor frequency range 0.01–70 MHz, corresponding to magnetic field strengths varying between 2.343×10^{-4} and 1.645 T (Figure 5). The NMRD profiles are typical of small Gd^{3+} chelates and show that the relaxivity of [Gd(1,4-Medo2ampa)] is higher than that of [Gd(1,7-Medo2ampa)] in the whole range of proton Larmor frequencies.

The paramagnetic effect of the Gd^{3+} ion on the ^{17}O chemical shifts of [Gd(1,7-Medo2ampa)] was found to be negligible. However, the transverse ^{17}O relaxation rates $1/T_{2r}$ increase with increasing temperature, which is typical of systems in the slow exchange regime (Figure 6). The temperature dependence of the $1/T_{2r}$ data measured for [Gd(1,4-Medo2ampa)] evidences a fast water-exchange regime in the whole temperature range investigated, although the data display a maximum at the low-temperature side that signals the commencement of a change-over from a fast water-exchange regime at high temperatures to a slow exchange regime. The temperature dependence of the reduced chemical shifts ($\Delta\omega_r$) measured for [Gd(1,4-Medo2ampa)] is in line with the $1/T_{2r}$ data.

A simultaneous analysis of the ^{1}H relaxivity and ^{17}O NMR data was performed using well-established procedures.[13] Given the large number of parameters that enter the fit of the

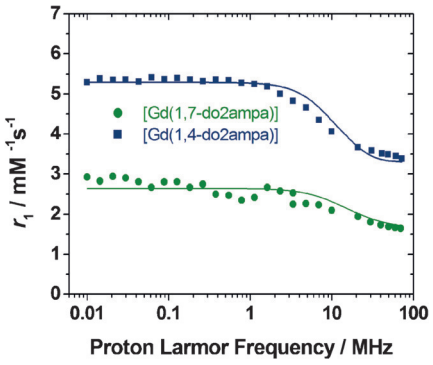

Figure 5. ^{1}H NMRD profiles recorded for [Gd(1,7-Medo2ampa)] and [Gd(1,4-Medo2ampa)] at 298 K. The solid lines represent the fits of the data as described in the text.

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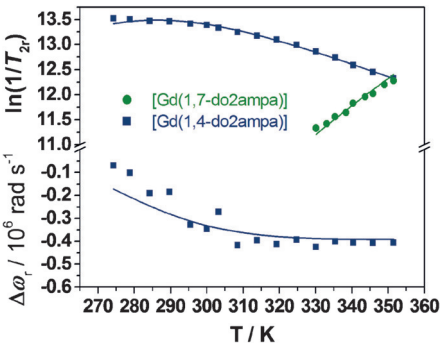

Figure 6. Reduced transverse ^{17}O relaxation rates and chemical shifts measured at 11.74 T (pH 7.2). The solid lines correspond to the fits of the data as described in the text. For [Gd(1,7-Medo2ampa)] the paramagnetic effect on T_2 was significant only at high temperatures owing to the slow water exchange, whereas effects in chemical shifts were negligible. The reduced relaxation rates and chemical shifts are defined as $1/T_{2r}=[1/(c_{Gd}/55.5)][1/T_i-1/T_{iA}]$ and $\Delta\omega_r=[1/(c_{Gd}/55.5)](\omega-\omega_A)$, in which T_i and T_{2A} are the paramagnetic and diamagnetic relaxation times, ω and ω_A are the paramagnetic and diamagnetic chemical shifts, and c_{Gd} is the concentration of the complex.

NMRD and ^{17}O NMR data, some of them had to be fixed to achieve a reliable analysis. The number of water molecules in the inner coordination sphere of Gd^{3+} was fixed to $q=1$ in [Gd(1,7-Medo2ampa)] on the basis of the luminescence measurements described above. However, the ^{17}O $1/T_{2r}$ and chemical shift data obtained for [Gd(1,4-Medo2ampa)] clearly point to an equilibrium involving a nine-coordinate species with one inner-sphere water molecule and an eight-coordinate $q=0$ species. This is in line with the hydration numbers obtained from luminescence-lifetime measurements for the complexes with Eu^{3+} and Tb^{3+} ions, which flank Gd^{3+} in the lanthanide series. Hydration equilibria were found to be relatively common in Gd^{3+} complexes. An accurate determination of the equilibrium constant at different temperatures was accomplished in some cases by analyzing the $^5D_0\leftarrow{}^7F_0$ transition observed in the absorption spectra of the Eu^{3+} analogues.[36] These studies provided hydration entropies of $\Delta S^\circ \approx 40\ J\,mol^{-1}\,K^{-1}$ for hydration equilibria defined in Equation (1):[37]

$$[Ln(L)(H_2O)] \rightleftharpoons [Ln(L)] + H_2O \qquad (1)$$

in which L represents a polyaminopolycarboxylate ligand and charges are omitted for simplicity. Thus, we included ΔS° and ΔH° for reaction (1) in [Gd(1,4-Medo2ampa)] as fitting parameters. The distance of closest approach for the outer-sphere contribution a_{GdH} was fixed at 4.0 Å, and the distance between the proton nuclei of the coordinated water molecule and the Gd^{3+} ion (r_{GdH}) was fixed to the values obtained from our DFT calculations (Table 2). The values of the ^{17}O hyperfine coupling constants ($A/\hbar$, Table 2) were fixed to the values estimated using DFT calculations following the previously reported methodology (TPSSh/SCRECP/EPR-III level).[29,38,39] Finally, the values of the activation energies for the diffusion coefficient (E_{DGdH}), the rotational correlation time (E_r), and the activation energy for the modulation of the zero-field-splitting (E_V) were fixed to common values (22, 20, and 1 kJ mol^{-1}, respectively).[13] The value of τ_R^{298} of [Gd(1,4-Medo2ampa)] was fixed to that obtained for [Gd(1,7-Medo2ampa)], a reasonable assumption considering the identical size of the two complexes.

The values obtained for the parameters determining the electron-spin relaxation (the electronic correlation time for the modulation of the zero-field-splitting interaction, τ_v, and the mean square zero-field-splitting energy, Δ^2) and the diffusion coefficient D_{GdH}^{298} are close to those reported for other Gd^{3+} complexes, and the values of the rotational correlation time are consistent with the size of the complexes (Table 2).[13]

The results of the fit obtained for [Gd(1,4-Medo2ampa)] provided a reaction enthalpy of $\Delta H^\circ = 5.7\pm3.0$ kJ mol^{-1} for reaction (1) and a reaction entropy of $\Delta S^\circ = 20.6\pm10.2$ J mol^{-1}, and defined a hydration number of 0.55 at 25 °C. This value is in very good agreement with the average of the hydration numbers determined for the Eu^{3+} and Tb^{3+} complexes (Table 1). The hydration number varies from 0.63 at the lowest temperature investigated (1 °C) to 0.55 at 78 °C. The positive ΔS° value is in line with values obtained for the hydration equilibria of different Eu^{3+} complexes.[37]

The parameters determined for the water exchange in [Gd(1,7-Medo2ampa)] ($k_{ex}^{298}=8.8\pm1.8\times10^3\ s^{-1}$, $\Delta H^{\neq}=51.9\pm4.4$ kJ mol^{-1}) provide a mean residence time of $\tau_m^{298}=114$ µs for the coordinated water molecule at 298 K. This value represents the lowest water-exchange rate of the coordinated water molecule for a Gd^{3+} complex, very similar to the one reported for the SAP isomer of $[Eu(dotam)(H_2O)]^{3+}$ (dotam = 2,2′,2″,2‴-

Table 2. Parameters obtained from the simultaneous analysis of the ^1H relaxivity and ^{17}O NMR data.

Parameter	1,7-Medo2ampa	1,4-Medo2ampa	dota^{4-}[a]	dotma^{4-}[b]
q^{298}	1.0	0.55	1.0	1.0
k_{ex}^{298} [10^3 s^{-1}]	8.8 ± 1.8	11 970 ± 3400	4100	11 800
τ_m^{298} [µs]	114	0.083	0.24	0.085
$\Delta H^{\neq}$ [kJ mol^{-1}]	51.9 ± 4.4	29.8 ± 3.3	49.8	44.5
$A/\hbar$ [10^6 rad s^{-1}]	−3.65[c]	−2.65[c]	−3.7	−3.7
τ_R^{298} [ps]	80 ± 27	80[c]	77	81
τ_V^{298} [ps]	15.9 ± 2.2	11.4 ± 1.7	11	7.9
Δ^2 [10^{19} s^{-2}]	9.96 ± 1.94	15.7 ± 3.4	1.6	1.7
r_{GdH} [Å]	2.918[c]	3.068[c]	3.1	3.1
D_{GdH}^{298} [10^{-10} m^2 s^{-1}]	21.9 ± 1.3	20.0[b]	20.2	22.4

[a] Data from Ref. [13]; [b] data from Ref. [41]. H_4dotma = α,α′,α″,α‴-tetramethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; [c] parameters estimated independently using DFT calculations.

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(1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl)tetraacetamide, $k_{ex}^{298} = 9.4 \times 10^3\ s^{-1}$),[40] and somewhat longer than those reported for Gd^{3+} complexes of dota-tetraamides ($9.9–330 \times 10^3\ s^{-1}$).[12] The very low water-exchange rates observed for dota–tetraamide complexes are explained in terms of the rather strong Gd–water interaction in +3-charged complexes that increases the energy cost for the departure of the water molecule in a dissociative activated exchange mechanism. Thus, the low water-exchange rate in [Gd(1,7-Medo2ampa)(H_2O)] is surprising considering the neutral charge of the complex. The inner-sphere water molecule in this complex occupies one of the coordination positions in one of the square faces of the square antiprism coordination polyhedron, whereas in dota-like complexes the water molecule is capping that square face. Thus, water molecules occupying the capping position provide weaker Gd–water bonds than water molecules in positions defining the square antiprismatic coordination. As a result, water molecules in the capping position are expected to experience faster water-exchange rates. This is confirmed by the fast water-exchange rate determined for [Gd(1,4-Medo2ampa)] ($k_{ex}^{298} = 1.2 \pm 0.3 \times 10^7\ s^{-1}$), which is approximately three times higher than that of $[Gd(dota)]^-$ and very similar to that reported for $[Gd(dotma)]^-$ (Table 2).[41] Both $[Gd(dota)]^-$ and $[Gd(dotma)]^-$ contain a water molecule coordinated in a capping position. However, the population of $[Gd(dotma)]^-$ in solution is dominated by the TSAP isomer (ca. 81%), whereas for $[Gd(dota)]^-$ the SAP isomer represents approximately 83% of the overall population. In both $[Gd(dota)]^-$ and $[Gd(dotma)]^-$ the exchange rate of the coordinated water molecule in the TSAP isomer was reported to be approximately seven times higher than in the SAP form. Thus, the extremely low water-exchange rate of [Gd(1,7-Medo2ampa)] must be related to the position that the water molecule occupies in the coordination polyhedron. We want to emphasize that the presence of a hydration equilibrium in [Gd(1,4-Medo2ampa)] introduces some uncertainty on the parameters obtained from the analysis of ^{17}O NMR and NMRD data. Nevertheless, our data provide clear evidence of a much faster water-exchange rate in [Gd(1,4-Medo2ampa)] than in [Gd(1,7-Medo2ampa)].

The labile capping bond phenomenon is in line with the water-exchange rates measured for a Gd^{3+} complex with a heptadentate triamide cyclen-based ligand. Monodentate binding of phosphate and acetate to this complex, presumably occupying a coordination position in one square face of the polyhedron, was shown to increase the water-exchange rate of the water molecule by two orders of magnitude.[42] These results also have an implication for the analysis of water-exchange rates of bis-hydrated complexes. For instance, the bis-hydrated complex [Gd(do3a)(H_2O)$_2$] (H_3do3a = 2,2′,2″-(1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetic acid) contains a water molecule coordinating at the apical position and a second water molecule at one of the vertexes of the SAP polyhedron. Previous computational studies suggested that these water molecules should present considerably different exchange rates,[32] although analysis of ^{17}O NMR data by using a three-site exchange model failed to provide individual exchange rates for the two coordinated water molecules.[43] Recently, Dolg and co-workers reported computational studies that pointed out that water molecules occupying capping positions within the Ln^{3+} coordination environment are inherently labile.[44] This phenomenon was attributed to environmental effects because the bond with a ligand occupying a capping position is hindered by the environment. Although these studies provided some hints pointing to the labile capping bond phenomenon, the study presented in this work provides unequivocal experimental evidence for this effect.

Conclusion

A rational design of two ligands with identical donor atoms sets allowed the tuning of the position of the coordinated water molecule, which occupies either a capping position or a position in one of the square faces of the square antiprismatic polyhedron. We found that, whereas [Gd(1,7-Medo2ampa)] contains a coordinated water molecule in aqueous solution, the [Gd(1,4-Medo2ampa)] analogue presents an equilibrium in solution involving $q = 1$ and $q = 0$ species. Nevertheless, the water-exchange rate measured for the fraction of complex containing a coordinated water molecule is three orders of magnitude higher than that of [Gd(1,7-Medo2ampa)]. Thus, the present contribution provides solid evidence demonstrating that water ligands occupying capping positions in the coordination polyhedron are intrinsically labile. The labile capping bond phenomenon demonstrated here represents a significant advance for the rational design of optimized Gd^{3+}-based contrast agents and CEST probes for MRI applications in clinical diagnostics and pre-clinical research. Furthermore, it is likely that this effect occurs not only in Ln^{3+} complexes but also in complexes with other metal ions, paving the way to a more rational control of the reactivity of metal complexes.

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